

Intra-Arterial Therapy as a Rescue Strategy after Clinically Failed Intravenous Thrombolysis May Increase the Likelihood of a Good Outcome in Patients with Severe Ischaemic Stroke

A Retrospective Two Centre Study

FEDERICO MENETTI¹, LUCA VERGANTI¹, ANDREA ZINI¹, STEFANO VALLONE¹,
PAOLO CARPEGGIANI¹, TOMMY ANDERSSON²

¹ Stroke Unit, Department of Neuroscience, "S. Agostino Estense" Hospital; Modena, Italy

² Karolinska University Hospital; Stockholm, Sweden

Key words: acute ischaemic stroke, rescue therapy, intravenous thrombolysis, intra-arterial treatment

Summary

The purpose of this study was to evaluate the efficacy and safety of intra-arterial therapy as a rescue strategy after clinically failed intravenous thrombolysis (IVT) in acute ischaemic stroke patients.

We conducted a retrospective analysis of consecutive acute ischaemic stroke patients treated with rescue therapy. The results from this study group were compared with those obtained from a control group consisting of 260 consecutive patients treated with IVT alone.

The study group consisted of 52 patients with a mean age of 63 years and a median NIHSS score at admission of 17. Recanalization was achieved in 92% with a symptomatic haemorrhage rate of 9.6%. Rescue patients admitted with a severe stroke (NIHSS score >12) had a significantly better outcome at 90 days compared to patients with the same score but treated with IVT alone. No difference was seen for patients with a lower score at admission.

This study indicates that rescue therapy may increase the proportion of patients with independent outcome if presenting with a severe stroke (NIHSS score >12) without increasing the rate of symptomatic haemorrhage.

Introduction

Reperfusion of the ischaemic brain is the most effective therapy for acute ischaemic stroke reducing the extension of the final infarct by preserving tissue at risk and thereby enabling a better clinical outcome¹⁻³. Intravenous thrombolysis (IVT) with Alteplase (recombinant tissue plasminogen activator; rt-PA) is currently the only approved therapy for treatment of acute ischaemic stroke^{4,5} but it has to be administered within 4.5 hours of symptom onset^{6,7}. In addition, the lytic potential of IVT is limited; recanalization is only achieved in < 1/3 of occluded proximal middle cerebral arteries and in very few (< 10%) internal carotid artery (ICA) terminus and basilar artery (BA) occlusions^{8,9}.

Consequently, in spite of proven clinical efficacy in large series, the numbers needed to treat (NNT) for IVT are high and >50% of the patients remain disabled or die⁵. To improve the recanalization rate, endovascular techniques such as intra-arterial thrombolysis (IAT)¹⁰⁻¹² or mechanical thrombectomy (MT)¹³⁻¹⁵ may be utilized to complement the intravenous therapy. The purpose of this study was to evaluate the efficacy and safety with such a com-

bined medical and minimally invasive endovascular approach.

Material and Methods

Consecutive acute ischaemic stroke patients treated with combined IVT and intra-arterial therapy between January 2009 and December 2010 at the Sant'Agostino Estense Hospital and at the Karolinska University Hospital were included in this retrospective analysis. The results from this study group were compared with those obtained from a control group consisting of 260 consecutive patients treated with IVT alone at the Comprehensive Stroke Unit in the same Italian hospital between January 2005 and December 2010.

All patients in the combined treatment group underwent computed tomography (CT), after which they were treated with full-dose (0.9 mg/kg) intravenous Alteplase (Actilyse®, Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany). Standard clinical criteria were applied to decide whether a patient was eligible for IVT and no infusion was started if the time from onset of symptoms exceeded 4.5 hours or if the initial CT scan revealed a haemorrhage or a large infarct (>1/3 of the MCA territory or extensive brain stem areas). After start of the infusion, the radiological protocol continued with CT angiography (CTA) if the patient was at a referring hospital. In case of a large vessel occlusion, the patient was transferred to the tertiary hospital (mainly the Karolinska University Hospital) with the infusion ongoing, where the patient was re-examined neurologically and a CT was repeated with the addition of CT perfusion (CTP)¹⁶.

In case the patient arrived directly at the tertiary centre, the radiological examinations were done sequentially with IVT administered after the CT had been rapidly analysed. No patient transfer, additional examinations or angio preparations at the tertiary centre extended the one hour that was needed for the full infusion which meant that groin puncture was consistently performed at the end of the infusion and final neurological examination. This means that intra-arterial therapy were recurrently performed slightly more than one hour after the start of IVT for all transferred patients. Directly admitted patients were positioned in the angio suite before the end of the infusion so that the final neurological examination was per-

formed with the patient on the angio table. The intra-arterial rescue therapy could then be immediately started or aborted which means that the time between the onset of IVT and intra-arterial therapy was consistently kept slightly more than one hour also for these patients. In two patients a clear clinical deterioration necessitated a repeat CT examination to rule out haemorrhagic or severely worsened ischaemic changes but this scan was performed at the end of the infusion and did not delay the start of the endovascular procedure. If the patient at the final neurological examination preceding the angiography had improved significantly, a repeat CTA was performed to verify a revascularization by IVT and the patient was excluded. All patients in the study group met the following criteria:

1. A National Institute of Health Stroke Scale (NIHSS) score of ≥ 6 .
2. An evident ischaemic penumbra as evaluated based on the initial CTP and the CTA source images.
3. Lack of clinical improvement after the infusion was finished (determined as an unchanged NIHSS score) *or* clinical deterioration without haemorrhagic or severely worsened ischaemic changes on a repeat CT scan.
4. Endovascular treatment could be started within eight hours of symptom onset.
5. The occlusion was located in a large artery regarded as possible to treat technically (ICA, MCA; first or second segment, basilar artery).

The intra-arterial therapy consisted of IAT (1) or mechanical thrombectomy (MT) (2).

1. IAT was performed with locally administered fibrinolytic drugs: rt-PA (maximum 20 mg) or Urokinase (maximum 1000000 IU) combined with careful mechanical manipulation and clot disruption by microcatheter and microguide wire.

2. MT was carried out utilizing the MERCI device (Concentric Medical/Stryker Neurovascular, Mountain View, CA, USA) or different so-called stent-retrievers: Solitaire FR (ev3 Endovascular, Plymouth, MN, USA/Covidien, Irvine, CA, USA), Trevo (Concentric Medical/Stryker Neurovascular), IRIIS (Mindframe, Irvine, CA, USA/Covidien), and Opticell (MindFrame/Covidien). Mechanical thrombectomy was performed using an 8 French balloon guide catheter (Concentric Medical) with aspiration.

All the angiographies at the time of thrombectomy were re-evaluated by two of the authors (LV and TA) and the rate of recanal-

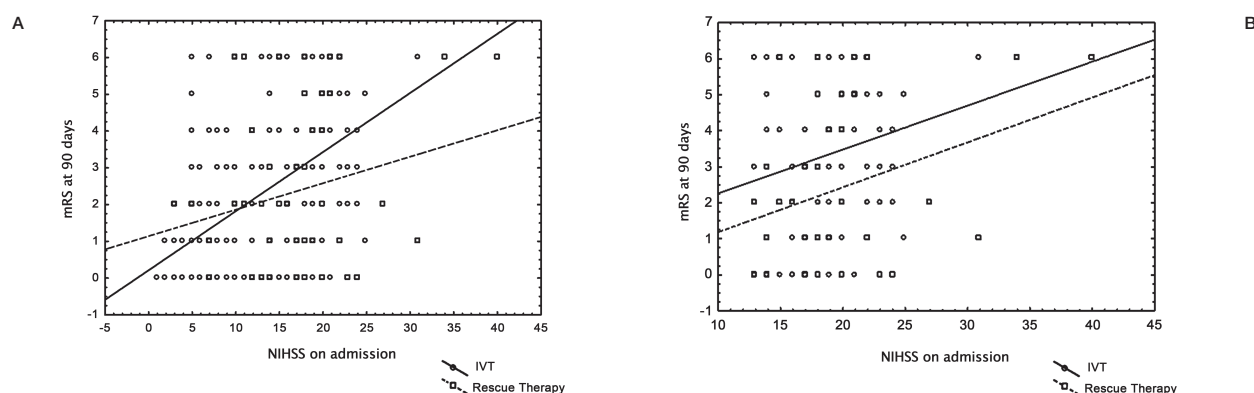


Figure 1 A) Scatterplot showing mRS at 90 days follow-up in relation to NIHSS at admission for *all patients in the study* treated with either IVT (solid line) or rescue therapy (dotted line). There was no significant difference between the groups even though endovascular therapy seemed beneficial for patients presenting with a high stroke score. B) Scatterplot showing mRS at 90 days follow-up in relation to NIHSS at admission *selectively for patients presenting with a NIHSS score of >12*. Rescue therapy patients (dotted line) presenting with such moderate to severe stroke consistently had a significantly better clinical outcome at 90 days compared with IVT patients (solid line) in a multivariate analysis ($p < 0.02$).

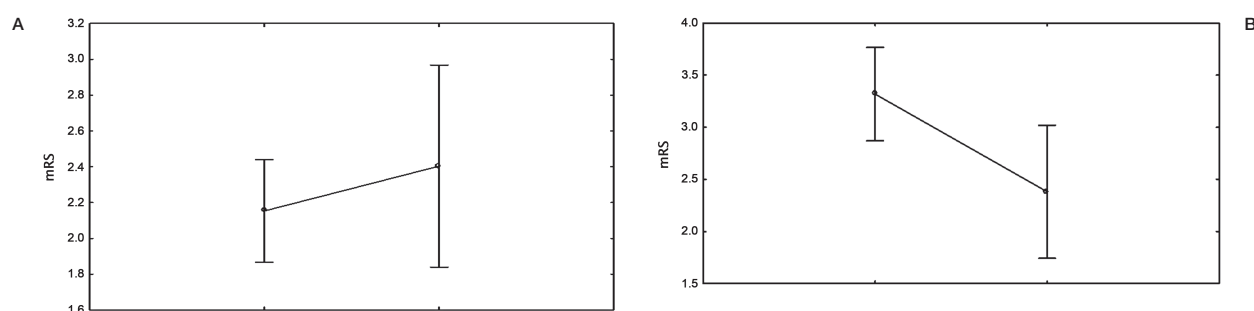


Figure 2 A) Analysis of variance for *all IVT and rescue therapy patients*, respectively, for mRS at 90 days - vertical bars show confidence intervals of 0.95. There was no significant difference between the groups with reference to outcome at 90 days. B) Analysis of variance *selectively for patients presenting with a NIHSS score >12* treated with IVT and rescue therapy, respectively, for mRS at 90 days - vertical bars show confidence intervals of 0.95. In this sub-group of moderate to severe stroke patients, intra-arterial rescue therapy led to a significantly better mRS outcome score at 90 days follow-up compared to IVT alone ($p < 0.02$).

zation quantified according to the Thrombolysis in Cerebral Infarction score (TICI, 17). TICI grade 0 was defined as no perfusion; grade 1 was defined as perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion; grade 2a was defined as perfusion of less than two-thirds of the vascular distribution of the occluded artery; grade 2b was defined as perfusion of two-thirds or more of the vascular distribution of the occluded artery; and grade 3 was defined as full perfusion with filling of all distal branches.

The functional outcome was scored at follow-up 90 days after treatment by an independent neurologist using the modified Rankin Scale (mRS). Good clinical outcome was defined as mRS 0-2. Safety was determined by classifying haemorrhagic transformations simi-

lar to the ECASS definition¹⁸ at the control CT scan performed 22-36 hours after treatment. The incidence of symptomatic bleeding was calculated defined as subarachnoid haemorrhage (SAH) or parenchymal haemorrhage type 2 (blood clot exceeding 30% of the infarcted volume with significant space-occupying effect) that were manifested in a clinical deterioration of >2 points on the NIHSS scale within 24 hours or causing death.

The 260 patients in the control group were treated with IVT within 4.5 hours of symptom onset in accordance with accepted practice, i.e. there were no exclusion criteria present and a CT scan ruled out intracranial haemorrhage and large ischaemic infarcts.

For the statistical analysis we used Statistica software (Version 9.1, Statsoft Inc, Tulsa, OK,

USA). For testing independence between outcome and exposure variables we used Pearson's Chi square tests (χ^2). We created scatterplots categorized by treatment option, and repeated-measures analysis of variance (ANOVA) was used on the whole sample for the two treatment groups. The local research ethics committee at both participating centres approved the study.

Results

A total of 52 patients were included in the study group. Approximately a third (17/52) of these patients were treated at the Sant'Agostino Estense Hospital, four with IAT and 13 with MT. The remaining two thirds (35/52) were treated at the Karolinska University Hospital, all with MT. Fifty-six per cent of the patients were male and 44% were female. The mean age was 63 years (range 16-83) and the median NIHSS score at admission was 17 (range 3-30). The baseline mRS (before stroke onset) was 0 for 89% of the patients, 1 for 8% and 2 for 3%. No patient had mRS >2 before treatment. Good or complete recanalization (TICI 2a-3) was achieved in 92.3% of the patients (48/52). Little or absent recanalization was obtained in 7.6% (4/52). Symptomatic intracerebral haemorrhage was discovered in the 24 hour CT scan in 9.6% of the patients (5/52) whereas the remaining patients had no or asymptomatic haemorrhages including also minimal contrast stain indicative of a rupture of the blood brain barrier. There were no device or procedure-related serious adverse events. At 90 days follow-up, 33 patients (63.4%) were independent with a good clinical outcome defined as a mRS score of 0-2 whereas ten patients (19.2%) had a poor outcome with a mRS score of 3-5. Mortality at

90 days was 17.3% as nine of the 52 patients had died (mRS=6).

There were no demographic differences comparing the study and control groups regarding age, gender and severe comorbidities, but the median NIHSS score at admission was 12 (2-30) in the control group. In this group treated with IVT alone, 59.2% (154/260) of the patients were ranked as having a good outcome (mRS 0-2) at 90 days follow-up; 29.6% (77/260) received a score of 3-5 and 11.2% (29/260) were dead. The proportion of clinically significant, symptomatic bleedings (SAH or PH-2) evaluated at the control CT performed 24 hours after drug administration, was 11.2% (29/260).

Based on the NIHSS score at admission, all patients were sub-grouped into three categories: A) NIHSS 1-7 ("minor stroke"), B) NIHSS 8-14 ("moderate stroke") and C) NIHSS \geq 15 ("severe stroke"). An analysis of the outcome in relation to NIHSS at admission is presented in Table 1.

Analysis of variance including all cases showed no difference for good clinical outcome (mRS 0-2) at 90 days follow-up comparing study and control group patients (Figures 1A and 2A), whereas a significantly larger percentage of patients in the study group ($p<0.02$) had a good outcome when the analysis was restricted to patients with moderate/severe stroke (NIHSS score > 12) at admission (Figures 1B and 2B).

Discussion

Rescue therapy, i.e. intra-arterial therapy as an adjunct in case full dose IVT (0.9mg/kg) has not been clinically successful, can be offered and is therefore considered in many institu-

Table 1 Outcome at 90 days for patients presenting with minor (NIHSS score 1-7), moderate (NIHSS score 8-14) or severe (NIHSS score \geq 15) stroke in the study and control groups, respectively. There was a significant difference ($p<0.02$) between the study and control groups in the category "severe stroke".

mRS at 90 d	Study				Control			
	Minor stroke	Moderate stroke	Severe stroke	All Study	Minor stroke	Moderate stroke	Severe stroke	All Control
0-2	100%	66.7%	58.3%	63.4%	84.4%	63.3%	34.4%	59.2%
3-5	0%	16.7%	22.6%	19.2%	9.1%	31.3%	47.3%	29.6%
6	0%	16.7%	19.4%	17.3%	6.4%	7.8%	18.3%	11.2%
N=	4 (7.7%)	12 (23.0%)	36 (69.2%)	52	77 (29.6%)	90 (34.6%)	93 (35.6%)	260

tions today. The purpose of this study was to investigate whether such therapy is safe and efficient.

This study has several weaknesses. The majority of patients in the study group were treated at one of the participating institutions whereas all patients in the control group came from another one. This is due to the fact that Karolinska University Hospital is a tertiary centre where few patients are admitted directly and treated with IVT if eligible. Instead, most patients are transferred from referring hospitals with the IV infusion ongoing, the so-called “drip and ship” strategy.

The intra-arterial treatment consisted of various methods: intra-arterial thrombolysis as well as thrombectomy with the Merci retriever system and more modern stent retrievers. As the study was performed in a transition time between the Merci retriever and stent retrievers, this reflects the actual situation at the time. It was also difficult to include later patients as the strategy was changed in the Karolinska after 2010 so that IVT patients with large vessel occlusions were taken straight to the angio suite as soon as possible, without waiting for the outcome of the IVT.

Patients in the study group all had proven occlusions in large arteries as shown by CTA whereas the control patients were treated with IVT without knowing where the occlusion was located. This is a problem that our study shares with recently published randomized trials^{19,20}. Probably, many of the low score patients treated with IVT did not have a large vessel occlusion, whereas high score patients are more likely to have harboured such an occlusion. This may at least in part explain why there is no difference in outcome between the groups when comparing patients admitted with a low NIHSS score. As intra-arterial therapy is only offered to patients with large vessel occlusions, a better approach would be to only compare patients having such an obstruction and treated with IVT only or rescue therapy. This was actually done in a case-control study²¹ in which patients receiving IVT were continuously monitored with transcranial Doppler (TCD) and transferred to the angio suite for intra-arterial treatment in case of a persistent occlusion. These patients were then matched with two historic controls with similar clot location and score on the NIHSS scale treated with IVT alone and not experiencing recanalization as estimated on TCD. The rescue therapy group had better

recanalization as well as a better outcome with an increase in the likelihood of independence at three months.

Finally, patients in the Italian centre may or may not have been offered rescue therapy, which may be seen as an inclusion bias. The explanation for this is that the control group consists of patients treated with IVT from 2005 to 2010 and intra-arterial therapy was not offered to patients in the earlier time points, even with a high score at admission. Later, some patients were offered endovascular therapy depending on the availability of the interventionists. This may indeed be seen as an inclusion bias but less so as the selection of patients offered intra-arterial treatment was basically random. The complete treatment of the patients that only received IVT at this comprehensive stroke centre was also identical during the recruitment period.

The most important findings of this study are that rescue therapy seems to be safe and effective for patients with a NIHSS score of > 12 at admission. The rate of symptomatic haematomas at 9.6% is slightly higher than that seen in recent stent retriever studies²²⁻²⁴ but in line with studies in which the Merci retriever system was used²⁵. In addition, we also used a somewhat more strict definition of “symptomatic haemorrhage”, in comparison with more commonly used criteria, comprising also patients with SAH and only demanding a clinical deterioration of > 2 points on the NIHSS scale. This may also, at least partly, explain the high rate of symptomatic haemorrhages detected in the control group (11.2%). Another explanation may be that a relatively high percentage (35.6%) of the IVT patients presented with a severe stroke including a NIHSS score of ≥ 15 probably increasing the risk of a haemorrhagic conversion. That full-dose IVT followed by intra-arterial treatment is safe was demonstrated previously²⁶ even if this study failed to demonstrate any significant difference in outcome between rescue therapy and IV alone. No subgroups were analysed based on NIHSS score at admission. That the combination of IVT with intra-arterial thrombolysis is not only safe but also efficient was suggested in a recent meta-analysis²⁷. After pooling the results from 15 studies the estimates for recanalization, mortality and symptomatic haemorrhage were similar to the findings in our study whereas the percentage of patients with a favourable outcome was somewhat higher in the

present study compared to the pooled estimate in this meta-analysis. The present study indicates that rescue therapy may be beneficial for patients with acute ischaemic stroke presenting with a NIHSS score of >12. Such score is also indicative of a large vessel occlusion²⁸, something that was obviously proven for all study patients. Indeed, if a thrombus residing in the MCA exceeds a length of 8 mm, IVT seems to be of limited value to promote revascularization²⁹. Patients in the study group with a lower score at admission also had a high percentage of good outcomes but this was not different from patients in the control group.

Conclusion

Even though this study is a retrospective analysis with several weaknesses, it seems reasonable to suggest from the data that patients admitted with a severe stroke defined as a NIHSS score of >12, with a proven large vessel occlusion, and in which IVT has had no clinical effect at the end of the infusion, could be offered intra-arterial rescue therapy. If patients with a lower score but still with a large vessel obstruction should also be offered the same cannot be answered from this study but remains a possibility.

References

- 1 Wardlaw JM, Murray V, Berge E, et al. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2009; (4): CD000213.
- 2 Fields JD, Lutsep HL, Smith WS, et al. Higher degrees of recanalization after mechanical thrombectomy for acute stroke are associated with improved outcome and decreased mortality: pooled analysis of the MERCI and Multi MERCI trials. *Am J Neuroradiol*. 2011; 32 (11): 2170-2174. doi: 10.3174/ajnr.A2709.
- 3 Nogueira RG, Liebeskind DS, Sung G, et al. Predictors of good clinical outcomes, mortality, and successful revascularization in patients with acute ischemic stroke undergoing thrombectomy: pooled analysis of the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi MERCI Trials. *Stroke*. 2009; 40 (12): 3777-3783. doi: 10.1161/STROKEAHA.109.561431.
- 4 Wahlgren N, Ahmed N, Dávalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet*. 2007; 369 (9558): 275-282. doi: 10.1016/S0140-6736(07)60149-4.
- 5 Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet*. 2010; 375 (9727): 1695-1703. doi: 10.1016/S0140-6736(10)60491-6.
- 6 Wahlgren N, Ahmed N, Dávalos A, et al. Thrombolysis with alteplase 3-4.5 h after acute ischaemic stroke (SITS-ISTR): an observational study. *Lancet*. 2008; 372 (9646): 1303-1309. doi: 10.1016/S0140-6736(08)61339-2.
- 7 Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 h after acute ischemic stroke. *N Engl J Med*. 2008; 359 (13): 1317-1329. doi: 10.1056/NEJMoa0804656.
- 8 Kharitonova T, Thoren M, Ahmed N, et al. Disappearing hyperdense middle cerebral artery sign in ischaemic stroke patients treated with intravenous thrombolysis: clinical course and prognostic significance. *J Neurol Neurosurg Psychiatry*. 2009; 80 (3): 273-278. doi: 10.1136/jnnp.2008.150185.
- 9 Bhatia R, Hill MD, Shobha N, et al. Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action. *Stroke*. 2010; 41 (10): 2254-2258. doi: 10.1161/STROKEAHA.110.592535.
- 10 del Zoppo GJ, Higashida RT, Furlan AJ, et al. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT Investigators. *Stroke*. 1998; 29 (1): 4-11. doi: 10.1161/01.STR.29.1.4.
- 11 Furlan A, Higashida RT, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. *Stroke*. 1999; 28 (21): 2003-2011. doi: 10.1001/jama.282.21.2003.
- 12 Ogawa A, Mori E, Minematsu K, et al. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the middle cerebral artery embolism local fibrinolytic intervention trial (MELT) Japan. *Stroke*. 2007; 38 (10): 2633-2639. doi: 10.1161/STROKEAHA.107.488551.
- 13 Barreto AD, Alexandrov AV. Adjunctive and alternative approaches to current reperfusion therapy. *Stroke*. 2012; 43 (2): 591-598. doi: 10.1161/STROKEAHA.111.617902.
- 14 Gralla J, Brekenfeld C, Mordasini P, et al. Mechanical thrombolysis and stenting in acute ischemic stroke. *Stroke*. 2012; 43 (1): 280-285. doi: 10.1161/STROKEAHA.111.626903.
- 15 Bösel J, Hacke W, Bendszus M, et al. Treatment of acute ischemic stroke with clot retrieval devices. *Curr Treat Options Cardiovasc Med*. 2012; 14 (3): 260-272. doi: 10.1007/s11936-012-0172-y.
- 16 Turk A, Magarik JA, Chaudry I, et al. CT-perfusion-guided patient selection for endovascular treatment of acute ischemic stroke is safe and effective. *J Neurointerv Surg*. 2012; 4 (4): 261-265. doi: 10.1136/neurintsurg-2011-010067.
- 17 Higashida RT, Furlan AJ, Roberts H, et al. Trial design and reporting standards for intraarterial cerebral thrombolysis for acute ischemic stroke. *Stroke*. 2003; 34 (8): e109-137. doi: 10.1161/01.STR.0000082721.62796.09.
- 18 Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet*. 1998; 352 (9136): 1245-1251. doi: 10.1016/S0140-6736(98)08020-9.
- 19 Broderick JP, Palesch YY, Demchuk AM, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med*. 2013; 368 (10): 893-903. doi: 10.1056/NEJMoa1214300.

- 20 Ciccone A, Valvassori L, Nichelatti M, et al. Endovascular treatment for acute ischemic stroke. *N Engl J Med*. 2013; 368 (10): 904-913. doi: 10.1056/NEJMoa1213701.
- 21 Rubiera M, Ribo M, Pagola J, et al. Bridging intravenous-intra-arterial rescue strategy increases recanalization and the likelihood of a good outcome in nonresponder intravenous tissue plasminogen activator-treated patients: a case-control study. *Stroke*. 2011; 42 (4): 993-997. doi: 10.1161/STROKEAHA.110.597104.
- 22 Dávalos A, Pereira VM, Chapot R, et al. Solitaire group. Retrospective multicenter study of Solitaire FR for revascularization in the treatment of acute ischemic stroke. *Stroke*. 2012; 43 (10): 2699-2705. doi: 10.1161/STROKEAHA.112.663328.
- 23 Saver JL, Jahan R, Levy EI, et al. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. *Lancet*. 2012; 380 (9849): 1241-1249. doi: 10.1016/S0140-6736(12)61384-1.
- 24 Nogueira RG, Lutsep HL, Gupta R, et al. Trevo versus Merci retrievers for thrombectomy revascularization of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomized trial. *Lancet*. 2012; 380 (9849): 1231-1240. doi: 10.1016/S0140-6736(12)61299-9.
- 25 Smith WS, Sung G, Saver J, et al. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. *Stroke*. 2008; 39 (4):1205-1212. doi: 10.1161/STROKEAHA.107.497115.
- 26 Bhatia R, Shobha N, Menon BK, et al. Combined full-dose IV and endovascular thrombolysis in acute ischemic stroke. *Int J Stroke*. 2012; doi: 10.1111/j.1747-4949.2012.00890.x. [Epub ahead of print]. doi: 10.1111/j.1747-4949.2012.00890.x.
- 27 Mazighi M, Meseguer E, Labreuche J, et al. Bridging therapy in acute ischemic stroke: a systematic review and meta-analysis. *Stroke*. 2012; 43 (5): 1302-1308. doi: 10.1161/STROKEAHA.111.635029.
- 28 Fischer U, Arnold M, Nedeltchev K, et al. NIHSS score and arteriographic findings in acute ischemic stroke. *Stroke*. 2005; 36 (10): 2121-2125. doi: 10.1161/01.STR.0000182099.04994.fc.
- 29 Riedel CH, Zimmermann P, Jensen-Kondering U, et al. The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. *Stroke*. 2011; 42 (6): 1775-1777. doi: 10.1161/STROKEAHA.110.609693.

Tommy Anderson, MD, PhD
Department of Neuroradiology
Karolinska University Hospital
Karolinska vägen 1
Stockholm SE-17176, Sweden
Tel.: 46-73-9661917
E-mail: tommy.andersson@karolinska.se